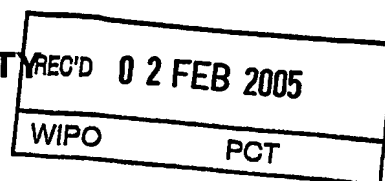




## PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY  
(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)



|   |  |  |
|---|--|--|
| Applicant's or agent's file reference<br>428 WO   | <b>FOR FURTHER ACTION</b><br>See Form PCT/PEA/416  |  |
| International application No.<br>PCT/DK2004/000162  | International filing date (day/month/year)<br>12.03.2004   | Priority date (day/month/year)<br>14.03.2003 |
| International Patent Classification (IPC) or national classification and IPC<br>C07C271/28, C07C233/43, A61P25/08, A61K31/167, A61K31/325   |  |  |
| Applicant<br>H. LUNDBECK AS   |  |  |
| <p>1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 7 sheets, including this cover sheet.</p> <p>3. This report is also accompanied by ANNEXES, comprising:</p> <p>a. <input type="checkbox"/> sent to the applicant and to the International Bureau a total of sheets, as follows:</p> <p><input type="checkbox"/> sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).</p> <p><input type="checkbox"/> sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.</p> <p>b. <input type="checkbox"/> (sent to the International Bureau only) a total of (indicate type and number of electronic carrier(s)), containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).</p> |  |  |
| <p>4. This report contains indications relating to the following items:</p> <p><input checked="" type="checkbox"/> Box No. I Basis of the opinion</p> <p><input type="checkbox"/> Box No. II Priority</p> <p><input checked="" type="checkbox"/> Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</p> <p><input type="checkbox"/> Box No. IV Lack of unity of invention</p> <p><input checked="" type="checkbox"/> Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</p> <p><input checked="" type="checkbox"/> Box No. VI Certain documents cited</p> <p><input type="checkbox"/> Box No. VII Certain defects in the international application</p> <p><input checked="" type="checkbox"/> Box No. VIII Certain observations on the international application</p>   |  |  |
| Date of submission of the demand<br><br>21.09.2004  | Date of completion of this report<br><br>01.02.2005  |  |
| Name and mailing address of the international preliminary examining authority:<br><br> European Patent Office<br>D-80298 Munich<br>Tel. +49 89 2399 - 0 Tx: 523656 epmu d<br>Fax: +49 89 2399 - 4465   | Authorized Officer<br><br>Bueno Torres, M<br><br>Telephone No. +49 89 2399-8290<br><br> |  |

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**Box No. I Basis of the report**

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.
  - ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
    - ☐ international search (under Rules 12.3 and 23.1(b))
    - ☐ publication of the international application (under Rule 12.4)
    - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)
2. With regard to the **elements\*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report):*

**Description, Pages**

1-84 as originally filed

**Claims, Numbers**

1-24 as originally filed

- ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing
3. ☐ The amendments have resulted in the cancellation of:
    - ☐ the description, pages
    - ☐ the claims, Nos.
    - ☐ the drawings, sheets/figs
    - ☐ the sequence listing (*specify*):
    - ☐ any table(s) related to sequence listing (*specify*):
  4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
    - ☐ the description, pages
    - ☐ the claims, Nos.
    - ☐ the drawings, sheets/figs
    - ☐ the sequence listing (*specify*):
    - ☐ any table(s) related to sequence listing (*specify*):

\* If item 4 applies, some or all of these sheets may be marked "superseded."

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**Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

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1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:
- ☐ the entire international application,
  - ☒ claims Nos. 18-24  
because:
    - ☒ the said international application, or the said claims Nos. 18-24 relate to the following subject matter which does not require an international preliminary examination (specify):  
**see separate sheet**
    - ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
    - ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
    - ☐ no international search report has been established for the said claims Nos.
    - ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:
      - the written form ☐ has not been furnished
      - ☐ does not comply with the standard
      - the computer readable form ☐ has not been furnished
      - ☐ does not comply with the standard
    - ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.
  - ☐ See separate sheet for further details

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**Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

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1. Statement

|                               |             |                             |
|-------------------------------|-------------|-----------------------------|
| Novelty (N)                   | Yes: Claims | 4, 7, 8, 11-12, 16, 18-24   |
|                               | No: Claims  | 1-3, 5, 6, 9, 10, 13-15, 17 |
| Inventive step (IS)           | Yes: Claims |                             |
|                               | No: Claims  | 1-24                        |
| Industrial applicability (IA) | Yes: Claims | 1-17                        |
|                               | No: Claims  |                             |

2. Citations and explanations (Rule 70.7):

**see separate sheet**

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**Box No. VI Certain documents cited**

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1. Certain published documents (Rule 70.10)

and /or

2. Non-written disclosures (Rule 70.9)

**see separate sheet**

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**Box No. VIII Certain observations on the international application**

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The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

**see separate sheet**

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**Re Item III.**

For the purpose of this communication it has been considered that the priority date of 14.03.03 has been validly claimed. If this were not the case document D12 could become relevant at the regional phase.

**Re Item V**

**Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. The following documents are referred to in this communication:

- D1: WO 02/18318 A (WELLA AKTIENGESELLSCHAFT, GERMANY) 7 March 2002 (2002-03-07)
- D2: WO 00/39118 A (ELI LILLY AND CO., USA; KYLE, JEFFREY, ALAN; ET AL.) 6 July 2000 (2000-07-06)
- D3: EP-A-0 515 684 (CHUGAI PHARMACEUTICAL CO., LTD., JAPAN) 2 December 1992 (1992-12-02)
- D4: EP-A-0 386 452 (BASF A.-G., GERMANY) 12 September 1990 (1990-09-12)
- D5: PORRETTA, GIULIO CESARE ET AL: "Research on antibacterial and antifungal agents. II. Synthesis and antifungal activity of new (1H-imidazol-1-ylmethyl)benzenamine derivatives" EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY, vol. 23, no. 4, 1988, pages 311-317, XP002286080
- D6: DATABASE CHEMABS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; SCALZO, M. ET AL: "Studies on substances with antibacterial and antifungal activity. I. Synthesis and microbiological activity of imidazolylmethylaniline derivatives" XP002286084 retrieved from STN Database accession no. 1986:221893
- D7: MEYER, WALTER E. ET AL: "N2-(4-Substituted-2,6-dichlorophenyl)-N1, N1-dimethylformamides as antihypertensive and diuretic agents" JOURNAL OF MEDICINAL CHEMISTRY, vol. 27, no. 12, 1984, pages 1705-1710, XP002286081
- D8: DAVOLL, JOHN ET AL: "Antimalarial drugs. 24. Folate antagonists. 2. 2,4-Diamino-6-[[aralkyl and (heterocyclic)methyl]amino]quinazolines, a novel

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class of antimetabolites of interest in drug-resistant malaria and Chagas' disease" JOURNAL OF MEDICINAL CHEMISTRY, vol. 15, no. 8, 1972, pages 812-826, XP002286082

D9: WO 01/09612 A (DRESDEN ARZNEIMITTEL) 8 February 2001 (2001-02-08)

D10: J. K. SEYDEL ET AL: J. MED. CHEM., vol. 37, no. 19, 1994, pages 3016-3022, XP002286083

D11: DATABASE BEILSTEIN BEILSTEIN INSTITUTE FOR ORGANIC CHEMISTRY, FRANKFURT-MAIN, DE; XP002286108 Database accession no. 6440745, 6442496 and 6444607.

2. The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-3, 5, 6, 9, 10, 13-15 and 17 is not new in the sense of Article 33(2) PCT.

Compound 72 of D4 falls within the definition of claims 1-3, 5, 6, 9, 10, 13-15 and 17 of the present application.

Compound XXII of D6 falls within the definition of claims 1-3, 5, 6, 9, 10, 13-14 of the present application. Said compound has been excluded in claim 17 by means of a proviso.

The compounds disclosed in D11 fall within the definition of claims 1-3, 5, 6, 10, 14 and 15 of the present application.

3. The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 1 does not involve an inventive step in the sense of Article 33(3) PCT.

The document D9 is regarded as being the closest prior art to the subject-matter of the present application, and discloses the compound retigabine in connection with opening activity of the KCNQ family potassium ion channels.

The compounds according to claim 1 differ from the known compound retigabine due to the presence of a CH<sub>2</sub> NH group instead of a NHCH<sub>2</sub> group at the para

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position of the aniline moiety.

The problem to be solved by the present invention may therefore be regarded as the provision of further aniline derivatives with opening activity of the KCNQ family potassium ion channels

Having regard for the above mentioned minor structural differences the qualitative activity of the present compounds as openers of the KCNQ family potassium ion channels is regarded as obvious. Therefore, in the absence of any non obvious or improved properties over the known compound retigabine, the subject-matter of claims 1-24 of the present application cannot be considered as involving an inventive step (Article 33(3) PCT).

VI. D12: EP-A-1 369 420 (AVENTIS PHARMA DEUTSCHLAND G.M.B.H., GERMANY; AJINOMOTO CO., INC.) (see paragraph [0095] on page 18

Filing Date: 06.06.02

Date of publication: **10.12.03**

VIII. The expression "aryl" has not been given the usual meaning to the person skilled in the art, since it also encompasses "**optionally substituted**" aryl and **heteroaryl** (see page 40 of the present application) (Art. 6 PCT).

The last compound of the proviso in claims 1 and 17 appears to have been repeated twice.